

When the above examples, other pterins replace sepiapterin, especially reduced pterins, e.g., (6R)-5,6,7,8-tetrahydro-L-biopterin, 7,8-dihydro-L-biopterin or 7,8-dihydro-D-neopterin, or 5,6,7,8-tetrahydro-D-neopterin or dihydrofolic acid or tetrahydrofolic acid or D,L-6-methyl-5,6,7,8-tetrahydropterin or 2-amino-6,7-dimethyl-4-hydroxy-5,6,7,8-tetrahydropteridine, similar guanosine triphosphate pathway blocking results are obtained and in same cases the reduced pterins also act as substrates for the pterin salvage pathway.

When in the above examples, other dihydrofolate reductase inhibitors replace methotrexate, e.g. aminopterin or 10-propargyl-5,8-dideazafolate or 2,4-diamino,5-(3',4'-dichlorophenyl),6-methylpyrimidine trimetrexate, or pyrimethamine or trimethoprim or pyritrexim 5,10-dideazatetrahydrofolate or 10-ethyl,10-deaza-aminopterin, similar results of pterin salvage pathway blocking are obtained.

When other pressor agents are substituted for phenylephrine in Example XI, e.g., angiotensin II, norepinephrine or thromboxane analogs (i.e., u46619) similar results are obtained to those obtained in Example XI.

EXAMPLE XIII

Over time DAHP depletes tetrahydrobiopterin in the brain but more slowly than in the periphery (i.e., outside the brain). This example is directed to ameliorating effects of any tetrahydrobiopterin depletion in the brain in the course of the inventions herein.

Groups of Sprague-Dawley rats (6–10 per group) are injected intraperitoneally with a bolus of levodopa (20 mg/kg) and L-5-hydroxytryptophane (10 mg/kg) in saline.

The groups of rats are immediately thereafter injected i.p. with DAHP (1 g/kg) in the one case and with MTX (10 mg/kg) in another case and with LPS (15 mg/kg) in both cases.

After 12 hours, the animals are anesthetized with ether and blood nitrate levels are reduced more than 50%.

Another group of rats is given LPS (15 mg/kg) only.

Another group of rats is given MTX (10 mg/kg) and LPS (15 mg/kg) only.

Another group of rats is given DAHP (1 g/kg) and LPS (15 mg/kg) only.

In the cases where MTX and DAHP are injected, nitric oxide levels are reduced more than 50% compared to where LPS is given alone, significantly reducing the fall in blood pressure from LPS administration.

In the cases where levodopa and L-5-hydroxytryptophane are administered, symptoms resulting from catecholamine and serotonin depletion are significantly attenuated.

In another case the levodopa is administered at 5 mg/kg together with carbidopa (at a weight ratio of levodopa:carbidopa of 10:1). Similar results of reduction of symptoms resulting from catecholamine and serotonin depletion are obtained.

In another case, the LPS is administered one hour before the levodopa and L-5-hydroxytryptophane instead of concurrently with the DAHP and MTX. There is somewhat less of a reduction in fall in blood pressure compared to concurrent administration but still a significant improvement compared to where LPS is administered alone.

In still another case, the LPS is administered 3 hours before the levodopa and L-5-hydroxytryptophane instead of concurrently with the DAHP and MTX and the DAHP and

MTX are administered alone and together with 20 mg/kg of N^G-methyl-L-arginine and in another case the N^G-methyl-L-arginine is administered without DAHP and MTX. For the case where MTX and DAHP are administered together with N^G-methyl-L-arginine, there is a significant improvement in reducing the fall in blood pressure from the LPS administration compared to where N^G-methyl-L-arginine is administered without DAHP or MTX and compared to where DAHP and MTX are administered without N^G-methyl-L-arginine and there are no deaths.

EXAMPLE XIV

A human is continuously administered interleukin-2 (10⁶ units) for 5 days. Levodopa and L-5-hydroxytryptophane are respectively administered by continuous infusion all during this period at respective levels of 20 mg/kg/day and 10 mg/kg/day. DAHP (1 g/kg/day) or MTX (10 mg/kg/day) is administered by continuous infusion. The severe hypotension and vascular leak characteristic of the end of interleukin-2 therapy are significantly reduced. Neurological symptoms are mild.

EXAMPLE XV

Pithed Sprague-Dawley rats are injected intraperitoneally first with levodopa (20 mg/kg) and L-5-hydroxytryptophane (10 mg/kg) and then with LPS (15 mg/kg) alone or together with DAHP (300 mg/kg). After 3 hours LPS causes a dramatic fall in blood pressure but less so in animals given DAHP. At this time, a bolus injection of phenylephrine (6 µg/kg) is able to elicit a significant pressor response in animals treated with DAHP but less of a pressor response in animals not treated with DAHP. The injection of DAHP and phenylephrine significantly overcomes the fall in blood pressure caused by LPS administration.

EXAMPLE XVI

Sprague-Dawley rats are injected with 25 cc air subdermally in the dorsal area in accordance with the air pouch inflammatory model (Selye, H., Proc. Soc. Exper. Biol. and Med., 82, 328–333 (1953)). Into the air pouch formed, an inflammatory stimulus, croton oil (0.5% in 0.5 ml corn oil), is injected. Simultaneously, the rats in one group are administered i.p. DAHP (0.3 g/kg) plus MTX (5 mg/kg) and this administration is repeated every 12 hours for 5 days. The rats administered DAHP plus MTX are also administered i.p. with levodopa (20 mg/kg/day) and L-5-hydroxytryptophane (20 mg/kg/day). At the end of the 5 days, the group of rats given DAHP and MTX have significantly less nitrite in the fluid exudate contained in the granulomatous lesion, less nitric oxide synthase activity in a homogenate of the granulomatous tissue and less inflammation than the rats in the other group. Neurological symptoms are mild.

In another case, the DAHP, MTX, levodopa and L-5-hydroxytryptophane are injected i.p. with the same daily doses except starting 2 days after the injection of air and croton oil. The inflammation is significantly improved at the end of 5 days, but not as much as in the case where DAHP plus MTX is given starting at the time of injection of air and croton oil.

Many variations of the above will be obvious to those skilled in the art. Thus, the invention is defined by claims. What is claimed is:

1. A method of inhibiting nitric oxide synthesis from arginine in vascular cells in a subject suffering from vascular dysfunction because of pathological overproduction of nitric oxide from arginine induced in said cells by cytokines and/or